amendments, as well as a clean version of the specification paragraphs and claims encompassing the amendments, is attached hereto.

The specification has been amended at page 4, lines 20, 21 and 29 and at page 8 lines 2 and 3, to correct obvious errors. At lines 21, 29 and 3 mentioned above, the term "2-cyanoethyl phosphate" has been corrected to read -- 2-cyanoethyl --. Applicants gratefully acknowledge the Examiner's identification of the term 2-cyanoethyl phosphate as technically incorrect and have replaced the term above, in the specification, in claim 15, and in claim 6 in accordance with the Examiner's suggestion. A review of page 5 of the specification clearly reveals that Applicants wished to refer to 2-cyanoethyl protecting groups.

At line 20, mentioned above, Applicants have inserted the word -- elimination -- following "β-" so that the term correctly reads "β-elimination", as it does in the claims and in other portions of the specification, such as at page 8, line 4. Finally, at line 2, as mentioned above, Applicants have simply deleted the typographical error "a" following the word "achieve".

Applicants submit that the above amendments clearly and correctly convey the Applicants' intended meanings. Thus, the above amendments to the specification correct obvious errors. Therefore, appropriate correction has been requested.

35 U.S.C. § 112, SECOND PARAGRAPH REJECTION OF CLAIM 6

Claim 6 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Specifically, the Examiner objects to the term "a 2-cyanoethyl phosphate group" because

it incorrectly implies a group containing a diphosphate linkage. The incorrect term also appears in claim 15.

In response to the above rejection, Applicants have amended claims 6 and 15 above to delete the term "2-cyanoethyl phosphate" and substitute -- 2-cyanoethyl --, in accordance with the Examiner's suggestion. Therefore, the basis for the above rejection as applied to claim 6 has been eliminated. Thus, Applicants respectfully request that the above rejection be withdrawn.

35 U.S.C. § 103(a) REJECTION OF CLAIMS 1-15

Claims 1-15 are rejected under 35, U.S.C. § 103(a) as being unpatentable over Isis Pharmaceuticals, EP 1 028 124 (hereinafter "Isis") in view of Hsiung et al. Nucleic Acids Research, vol. 11, number 10, 3227-39 (May 25, 1983) (hereinafter "Hsiung"). Applicants respectfully traverse this rejection for the reasons set forth below.

Applicants submit that the primary reference Isis, does not qualify as prior art under any paragraph of 35, U.S.C. § 102. Therefore, the Isis reference does not properly support a prima facie case of obviousness, either alone or in combination with a secondary reference. Applicants respectfully point out that in accordance with MPEP § 2127, paragraph III, the Isis reference cannot be relied upon as prior art until August 16, 2000, it date of publication, which follows the filing date of the instant application. Applicants acknowledge that the Isis reference, EP 1 028 124, claims priority to U.S. application 118564 P, filed February 4, 1999, and appreciate the Examiner's effort in bringing this to their attention.

The Hsiung reference discloses the use of organic amines, including diethylamine, to remove cyanoethyl moieties from triesters that are intermediates in a non-solid-support oligonucleotide synthesis. Hsiung neither discloses, nor even suggests the instant invention wherein oligonucleotide is attached to a substrate and the phosphate protecting groups are removed without detaching the oligonucleotide form the substrate.

In view of the above deficiencies of the cited references alone or in combination, the presently claimed invention is patentably nonobvious over the prior art. Thus, it is respectfully requested that the above rejection be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

Stephen G. Ryan, 39,015
Attorney for Applicants

Amersham Pharmacia Biotech, Inc.
800 Centennial Avenue
P. O. Box 1327
Piscataway, NJ 08855-1327

Tel: (732) 457-8071
Fax: (732) 457-8463

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 9-6-01

Melissa Leek
Signature
Date September 6, 2001

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Specification (marked-up version showing amendment(s))

The paragraph at page 4, lines 20-25:

Preferably, the phosphate protecting group is a group capable of undergoing β-elimination, such as 2-cyanoethyl[phosphate]. The reagent cleaves the phosphate protecting group from the oligonucleotide by β-elimination. Preferably, the reagent comprises an amine with a formula R-N-R_1R_2 wherein R, R_1 and R_2 are independently hydrogen, hydroxy, alkyl, allyl, aryl, cycloalkyl, alkenyl, alkoxy, allyloxy, aryloxy, and may include from one to twenty carbon atoms.

The paragraph bridging pages 4 and 5, beginning on page 4, line 26 and ending on page 5, line 2:

In particular, the instant disclosure pertains to a method for purifying an oligonucleotide that comprises providing an oligonucleotide containing a phosphate protecting group attached to a substrate, wherein the phosphate protecting group is 2-cyanoethyl[phosphate]; contacting the oligonucleotide with diethylamine to cleave the phosphate protecting groups from the oligonucleotide without detaching the oligonucleotide from the substrate; isolating the oligonucleotide attached to the substrate from the cleaved phosphate protecting groups; and contacting the oligonucleotide attached to the substrate with ammonium hydroxide to cleave the oligonucleotide from the substrate.

The paragraph bridging pages 7 and 8, beginning on page 7, line 27 and ending on page 8, line 12:

After completion of oligonucleotide synthesis using any available method such as phosphite triester and H-phosphonate chemistries, the substrate-bound oligonucleotide is treated with a reagent to selectively remove the phosphate protecting groups from the oligonucleotide backbone. The selection of reagent and conditions thereof is generally dependent on the ability of the reagent to selectively cleave the phosphate protecting groups in such a manner that the oligonucleotide still remains attached to the substrate. Any compound or enzyme that can achieve [a]this effect falls within the scope of the present disclosure. For example, many phosphate protecting groups such as 2-cyanoethyl [phosphate]are capable of undergoing β-elimination. Accordingly, any reagent capable of cleaving the phosphate protecting group from the oligonucleotide by β-elimination may be used. Organic amines such as primary, secondary or tertiary amines that can remove the phosphate protecting group without cleaving the oligonucleotide from the substrate are preferred. More preferred are amines with the formula R-N-R_1R_2, wherein R, R_1 and R_2 are independently hydrogen, hydroxy, alkyl, allyl, aryl, cycloalkyl, alkenyl, alkoxy, allyloxy, aryloxy, and may include from one to twenty carbon atoms. Most preferred are t-butylamine-methylamine and diethylamine, in particular a solution of about 20% v/v diethylamine in anhydrous acetonitrile.

Claims (marked-up version showing amendment(s))

6. (twice amended) The method of Claim 5, wherein the phosphate protecting group is a 2-cyanoethyl [phosphate]group.

15. (once amended) A method for purifying an oligonucleotide that comprises:

a) providing an oligonucleotide containing a phosphate protecting group attached to a substrate, wherein the phosphate protecting group is 2-cyanoethyl[phosphate];

b) contacting the oligonucleotide with diethylamine to cleave the phosphate protecting groups from the oligonucleotide without detaching the oligonucleotide from the substrate;

c) isolating the oligonucleotide attached to the substrate from the cleaved phosphate protecting groups; and

d) contacting the oligonucleotide attached to the substrate with ammonium hydroxide to cleave the oligonucleotide from the substrate.